REMARKS

Following entry of the foregoing amendments, claims 1, 4 to 6, 9 to 13, 21, 24, 25, 36, 37, and 101 will be pending in this patent application. Claim 1 has been amended, and claim 17 has been canceled, herein, without prejudice. No new claims have been added. Support for the amendments is found throughout the specification as originally filed, including, for example, paragraph 76.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Alleged Obviousness

Claims 1, 4 to 6, 9 to 13, 17, 21, 24, 25, 36, 37, and 101 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by published U.S. patent application number US 2004/0259247 ("the Tuschl application") in view of published U.S. patent application number US 2002/0162126 ("the Beach Application"), and Manoharan *et al.*, *Tetrahedron Letter*, 1995, 36, 3651-3654 ("the Manoharan article"). Applicants respectfully request reconsideration and withdrawal of this rejection because the cited references fail to describe or suggest the presently claimed oligomeric compounds, and therefore fail to render compositions comprising the compounds obvious.

To establish *prima facie* obviousness, the Patent Office must demonstrate that the cited prior art reference or combination of references teaches or suggests all the limitations of the claims.[1] Because obviousness is necessarily determined as of the time of invention, it is fundamental that the Office avoid using hindsight when assessing obviousness.[2] In this regard, the Supreme Court recently indicated in *KSR Int'l Co. v. Teleflex* that "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of

[1] *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).
[2] See e.g., *KSR Int'l Co. v. Teleflex*, 127 S.Ct. 1727, (2007) (warning against "the distortion caused by hindsight bias . . . and arguments reliant on *ex post* reasoning."); 35 U.S.C. § 103 (requiring determination of whether an invention "would have been obvious at the time the invention was made.").

necessity will be combinations of what, in some sense, is already known."[3] To avoid the trap of hindsight, a finding of obviousness therefore requires the Office to identify "a *reason* that would have prompted a person of ordinary skill in the relevant field to combine the [known] elements *in the way the claimed new invention does*."[4] In applying these principles to a case involving chemical compounds, the Federal Circuit held in *Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd* that "it remains necessary to identify some *reason* that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."[5] In this regard, if modification of an invention described in the prior art in the manner proposed by the Patent Office would render the prior art invention unsuitable for its intended purpose, then no reason would have existed for making the modification.[6]

The claims as amended herein recite, *inter alia*, compositions that comprise a complementary pair of siRNA oligomeric compounds that are not covalently linked to each other. At least one of the oligomeric compounds comprises a steroid conjugate moiety *attached to a 3'-terminal monomeric subunit* of the oligomeric compound.

The cited references, when considered individually or in combination, fail to describe or suggest such oligomeric compounds. Moreover, modification of the compounds described in the references in the manner proposed by the Office would render the resultant compounds inactive in RNAi. Specifically, as discussed in the response filed July 10, 2009, the Tuschl application contains no teaching or suggestion whatsoever of conjugation of steroid moieties to the ends of double-stranded siRNA molecules. Instead, the Tuschl application describes double-stranded RNA molecules that mediate target-specific RNA interference or other target-specific nucleic acid modifications, such as DNA methylation.[7] The Tuschl application states that the RNA molecules may contain at least one modified nucleotide analogue and indicates that possible

[3] *Id.*
[4] *Id.* (emphasis added).
[5] *Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (emphasis added).
[6] In re Gordon, 733 F.2d 900 (Fed. Cir. 1984).
[7] Paragraph 8.

modifications include sugar, backbone, and nucleobase modifications.[8] The Tuschl application fails to describe or suggest, however, modifying the duplex RNAs by attachment of one or more conjugate moieties, much less a steroid moiety, to a 3'-terminal monomeric subunit of at least one of the RNA molecules.

The Beach application similarly fails to describe or suggest conjugation of steroid moieties to the 3'-ends of double-stranded siRNA molecules. The Beach application instead provides a listing of methods known in the art for introduction of nucleic acids into cells, which include "lipid-mediated carrier transport."[9] Significantly, the Beach application does not teach or suggest *conjugation* of a lipid moiety to a double-stranded siRNA molecule, but indicates only that lipid-mediated transport mechanisms are one possible way that double-stranded RNAs can be introduced into cells. Moreover, the Beach application provides no teaching or suggestion that *conjugation* of lipid moieties to duplex RNA molecules would be a viable means for facilitating uptake of the molecules into cells. Upon review of the Tuschl and Beach applications, those skilled in the art therefore would have had no reason to conjugate one or more lipid moieties to siRNA molecules due to the fact that the combined teachings of the references provide no suggestion that such modifications would impart any desirable properties to the molecules while preserving their biological activity.

The Manoharan article fails to compensate for the deficiencies of the Tuschl and Beach applications. Notably, the Manoharan article describes incorporation of lipid-conjugated nucleosides into *single-stranded* antisense *DNA* oligonucleotides, which exert their biological activity by serving as substrates for RNase H. Significantly, the Manoharan article indicates that the lipid-conjugated nucleosides can be incorporated at *internal or 5'-terminal positions* of oligonucleotides, and the articles describes specific oligonucleotides in which the lipid-conjugated nucleosides were incorporated at the 5'-terminal position.[10] The article contains no teaching or suggestion, however, of incorporating the lipid-conjugated nucleosides at the *3'-terminal position* of oligonucleotides. Accordingly, based upon the description provided in the

[8] Paragraphs 15 to 16.
[9] Paragraph 139.
[10] Page 3652-3653.

Manoharan article, those skilled in the art would have had no reason to prepare antisense oligonucleotides containing 3'-congugate groups, much less siRNA duplexes containing 3'-congugate groups.

The Office asserts, however, that those skilled in the art would have combined the teachings of the Manoharan article regarding adding conjugate groups to antisense oligonucleotides, with the teachings of the Tuschl and Beach applications regarding chemical modification of siRNA molecules, and asserts that such a combination would have rendered obvious conjugation of cholesterol to the terminal positions of siRNA duplexes. Assuming for the sake of argument that those skilled in the art actually would have combined the teachings of these references, which applicants submit those skilled in the art would not have done for the reasons discussed at length in the response filed July 10, 2009, such a combination would have rendered the siRNA molecules described in the Tuschl and Beach applications unsuitable for RNA interferences. As understood by those skilled in the art,[11] blocking the 5'terminus of the antisense strand of siRNA duplexes abolishes the RNA interference activity of the molecules. Accordingly, if the teachings in the Manoharan article regarding adding conjugate groups to the 5' ends of antisense oligonucleotides would actually have led those skilled in the art to add conjugate groups to the 5' ends of siRNA molecules, the resultant siRNAs would not have exhibited RNA interference activity. Modification of the siRNA molecules described in the Tuschl and Beach applications in the manner proposed by the Patent Office – adding conjugate groups as taught by the Manoharan article - would therefore have rendered the siRNAs unsuitable for their intended purpose, and no reason therefore would have existed for making such modifications.

Based upon the combined teachings of the cited references, those of ordinary skill in the art thus would have had no reason to design and produce the claimed complementary pairs of siRNA oligomeric compounds consisting of first and second oligomeric compounds that are not covalently linked to each other in which at least one of the first and second oligomeric compounds comprises at least one steroid conjugate moiety attached to a 3'-terminal monomeric

[11] Schwarz, D.S., *et al.*, *Molecular Cell*, 10, 537-548, see page 539 (attached as Appendix A) and Martinez, J., *et al.*, *Cell*, 110, 563-574, see page 565 (attached as Appendix B).

subunit of the oligomeric compound. Compositions comprising such compounds therefore would not have been obvious at the time of the invention, and applicants accordingly, respectfully, request withdrawal of the rejection.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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